ACCESSION NUMBER: 1985:286950 BIOSIS
DOCUMENT NUMBER: BA79:66946
TITLE: MECHANISMS OF SYNERGISM BETWEEN GLUCOSE AND CYCLIC AMP ON STIMULATION OF **INSULIN** RELEASE.
AUTHOR(S): PHANG W; DOMBOSKI L; KRAUSZ Y; SHARP G W G
CORPORATE SOURCE: DEP. PHARMACOLOGY, NEW YORK STATE COLLEGE VET. MED., CORNELL UNIV., ITHACA, NY 14853.
SOURCE: AM J PHYSIOL, (1984 (RECD 1985)) 247 (6 PART 1), E701-E708. CODEN: AJPHAP. ISSN: 0002-9513.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The mechanism of synergism between glucose and adenosine cAMP on **insulin** release was studied. Synergism may result from inhibition of Na+-Ca2+ exchange by glucose and a cAMP-induced sensitization of the release machinery to Ca2+. To distinguish between these 2 possibilities, isolated rat pancreatic islets were perfused with agents that raise intracellular levels of cAMP [3-isobutyl-1-methylxanthine (IBMX) and forskolin] and others that increase intracellular concentrations of Ca2+ either by blocking Na2+-Ca2+ exchange (ouabain and choline-Ringer solution) or by causing increased Ca2+ influx (KCl, carbachol and 10 mM Ca2+). The combination of cAMP and increased Ca2+ influx or blocked Na2-Ca2+ exchange and increased Ca2+ influx potentiated **insulin** release. When the relative potentiating abilities of cAMP and blocked Na2+-Ca2+ exchange were compared by determining the individual effects of IBMX and 1 mM ouabain (a concentration that causes similar inhibition of 45Ca2+ efflux was 16.7 mM glucose) in the presence of carbachol, cAMP was only 1.4 times more potent as a potentiating agent than blocked Na+-Ca2+ exchange. The greatest potentiation of **insulin** release was observed when Na+-Ca2+ exchange was blocked in the presence of increased levels of intracellular cAMP.

ACCESSION NUMBER: 1989:68969 CAPLUS
DOCUMENT NUMBER: 110:68969
TITLE: Structural dependency of the inhibitory action of benzodiazepines and related compounds on the mitochondrial sodium-calcium exchanger
AUTHOR(S): Chiesi, Michele; Schwaller, Roland; Eichenberger, Kurt
CORPORATE SOURCE: Pharm. Div., Ciba-Geigy Ltd., Basel, Switz.
SOURCE: Biochem. Pharmacol. (1988), 37(22), 4399-403
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
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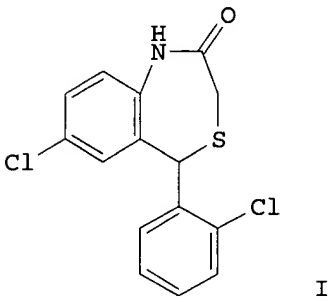

I

AB Na+-induced Ca2+-release from guinea pig heart mitochondria is inhibited by benzodiazepines such as clonazepam. The capacity of various related compds. to inhibit the rapid Ca2+ efflux induced by 20 mM Na+ was examd. The potency of inhibition was found to depend on several factors, such as 2'-halogen substitution and the presence of a secondary amido group. Very effective inhibitors were identified among the triazolo derivs. of benzodiazepines or obtained by replacing the diazepine ring by an oxazepine or a thiazepine. Some of these favorable structural modifications were compounded in the benzothiazepine 7-chloro-3,5-dihydro-5-phenyl-1H-4,1-benzothiazepine-2-on (I), which proved to be about 20 times more potent than the related compds. clonazepam and diltiazem. I has an IC50 in the submicromolar range, is the most potent selective inhibitor of the mitochondrial exchanger so far reported. The structural requirements found for the inhibition of the mitochondrial Na+-Ca2+ exchanger were quite distinct from those described for the binding of benzodiazepines to their central-type and peripheral-type sites.